High mortality among patients with tuberculosis accessing primary care facilities: secondary analysis from an open-label cluster-randomised trial

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Summary

Background Tuberculosis (TB) mortality remains persistently high, despite global TB control efforts. The aim of this study was to assess if a quality improvement (QI) intervention reduced deaths in TB patients accessing primary healthcare (PHC) services.

Methods In this pre specified secondary analysis of a cluster-randomized controlled study conducted in 2016–2018 in South Africa (Clinicaltrials.gov, NCT02654613), we compared 18-month case-fatality rates among newly diagnosed TB patients irrespective of HIV status randomized to clinics receiving the QI intervention and standard of care (SOC) [(eight clusters and 20 clinics per arm)]. Statistical inferences used a *t*-test from a two-stage approach recommended for cluster-randomized trials with fewer than 15 clusters per arm.

Findings Among the 5817 newly diagnosed TB patients enrolled (intervention = 3473; control = 2344), 562 died by 18-months [case-fatality rate (CFR) = 9·7%]. Ninety percent of the deaths (506/562) occurred within six months of TB treatment initiation. Quality improvement intervention arm clinics compared to control arm clinics did not demonstrate a significant difference in TB CFR. Case-fatality rates were 9·5% [95% Confidence Interval (CI): 6·9–12·9] and 11·3% (95% CI: 8·7–14·7) [adjusted rate ratio (aRR), 0·9 (95% CI: 0·6–1·2)] in the intervention and control arms, respectively. In people living with HIV/AIDS (PLWHA) CFR in the intervention and control arms: were 10·8% (95% CI: 7·8–14·7) and 14·4% (95% CI: 9·3–22·4) in those on antiretroviral therapy (ART) and 18·6 (95% CI: 9·1–38·0) and 33·0 (95% CI: 16·2–67·3), in those with no ART data respectively. In the intervention and control arms CFR in HIV-TB coinfected patients was 6·5 (95% CI: 3·6–11·6) and 11·5 (95% CI: 6·5–20·0) in those on ART with viral loads <200 copies/ml and 22·4 (95% CI: 16·7–30·2) and 19·7 (95% CI: 11·3–34·5) in those with no viral load data as they commenced ART within 12 months before initiating TB treatment, respectively.

Interpretation The quality improvement intervention did not significantly reduce mortality. *We observed that TB CFR was higher among PLWHA not on ART and HIV-TB coinfected patients.*

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Keywords: Quality improvement; TB case fatality rate; Mortality; HIV-TB coinfected mortality; Primary healthcare

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Research in context

Evidence before this study

We searched Medline via PubMed for articles published between 2003 and 2019 reporting on search terms: "epidemiology of HIV-TB co-infection"; "Tuberculosis mortality"; "Quality Improvement"; "resource-constrained"; 'HIV' AND tuberculosis, OR TB" yielding 290 relevant published articles that recommended additional interventions such as quality improvement (QI) targeting health systems performance improvements. Our search yielded two published trials the Merge trial found no effect on morbidity, mortality, and retention in care among newly diagnosed tuberculosis (TB) or human immunodeficiency virus (HIV) patients, and the TB-Fast Track trial found no short-term mortality reduction among people living with HIV/AIDS (PLWHA) despite substantial increases in TB diagnosis and treatment coverage. Evidence guiding effective implementation of comprehensive TB and HIV services to realise population level mortality benefits remains a key strategy in addressing persistently high TB mortality rates in resource limited settings.

Added value of this study

This study demonstrates that TB deaths occur in one in ten patients with a known TB diagnosis despite being linked to care. While we did not observe a significant reduction in TB case fatality rates in facilities implementing QI activities, we found higher case fatality rates in TB patients that were males older than 50 years, those residing in rural areas, and viremic PLWHA i.e. ART naïve, recently commencing ART, or unknown ART status.

Implications of all the available evidence

Ongoing TB mortality in known TB patients linked to care highlights the need for close clinical observation and early triage of patients at risk for TB mortality and TB related complications. Our findings support strategies to address groups at higher risk for mortality. Advocacy for greater demand for TB services and strengthened HIV/TB program implementation for rural clinics, older males and vulnerable PLWHA is necessary. Furthermore, this study highlights the need to strengthen HIV and TB service delivery in rural clinics through use of strategies such as QI interventions and regular outreach support.

Introduction

The World Health Organization's (WHO) vision to end tuberculosis (TB) as a global public-health threat by 2035 requires TB incidence and mortality reduction by 90% and 95% respectively. In an effort to accelerate progress toward these aspirational goals within the next decade latest evidence-based optimized treatment and prevention modalities, including improved diagnostic tools have been incorporated into global TB program guidelines. Despite these efforts to strengthen global TB control, TB mortality remains unacceptably high with approximately 1·25 million deaths occurring worldwide in 2023 alone.[1] Furthermore, compared to previous years, reversal in the annual decline in TB mortality observed in 2020 and 2021 coupled with failure to achieve a 35% reduction in TB mortality in 2020 compared to 2015 are deeply concerning global trends, possibly signaling inability to attain TB mortality targets set for 2035.[2,3]

It has been globally recognized that high-quality health systems enabling healthcare worker learning together with ongoing improvement interventions supporting safe, efficient, integrated, and patient-centered health service is essential to meet sustainable development goal-3.[4] Quality improvement (QI) for TB comprises a series of activities aimed at identifying and addressing performance gaps in each step of the TB care cascade. This includes training and capacity building of healthcare workers, in-person QI mentorship of clinic staff, and data driven QI interrogation of clinic processes that support activities in the TB care cascade. Gaps and failures are addressed to reach universal coverage targets for TB screening, testing, diagnosis, linkage to treatment, and favorable treatment outcomes.[5]

Published data from diverse settings provide clear evidence supporting QI intervention implementation within public health settings for improved population health. Quality improvement methodology was successfully implemented in South Africa to reduce mother-to-child transmission of Human Immunodeficiency Virus (HIV), improve HIV program data quality and for public sector antiretroviral therapy (ART) and prevention of mother-to-child transmission (PMTCT) program scale-up.[6–8] Performance gaps in the PMTCT pathway addressed using QI activities increased ART uptake in: antenatal attendees from 74% to 86%, women in labor from 10% to 25%, and overall intrapartum women from 43% to 84%.[7] Furthermore, QI supported data showed increases in data completeness and data accuracy of 38% and 28% respectively ($P < 0{\cdot}0001$).[6] Quality Improvement methods used to improve ART scale-up increased monthly HIV testing by 301·8% ($P < 0{\cdot}0001$), and monthly ART initiation by 185·5% ($P < 0{\cdot}0001$).[9]

Quality improvement interventions for comprehensive HIV and TB service delivery require both human and financial investments which may be lacking in resource limited disease endemic settings. High staff turnover and inadequate skills and capacity of newly deployed staff requires ongoing investments for delivery of comprehensive services. Conversely suboptimal implementation of services results in poorer population health and higher mortality.

Published literature from several resource constrained disease endemic settings demonstrates shortcomings in the TB care cascade, emphasizing the need for high-quality TB control programs to avert high mortality rates and achieve epidemic control.[5,10–14] Quality improvement is a recommended implementation strategy to close the gaps in the TB care cascade and scale up best practices to improve TB program outcomes.[11–15] Tuberculosis deaths are associated with multiple clinical, demographic, and social factors and is also highly dependent on quality of diagnostic and treatment services. Poor-quality TB care and non-utilization of healthcare services were found to be equal contributors to all TB deaths.[4] Consequently, improving quality of TB care and optimizing use of existing tools are simple strategies to avert TB deaths.

The Scaling Up TB and HIV Treatment Integration (SUTHI) randomized control study, assessed the impact of a QI intervention on HIV and/or TB associated mortality at 12 months follow-up in primary healthcare (PHC) clinics in South Africa. All-cause mortality rates in the intervention and control arms in HIV-TB co-infected patients was 10·1 and 9·8 per 100 person-years and in people living with HIV/AIDS (PLWHA) only was 2·6 and 2·2 respectively.[14] Secondary analysis evaluating use of QI interventions to address gaps in process indicators within the TB care cascade showed increased: TB symptom screening by > 80%, HIV testing by 19%, and initiation of TB preventive therapy (TPT) by 66%.[5]

We hypothesized that the QI intervention will have the highest impact on case fatality rates (CFR) between three and 12 months after randomization. Follow-up beyond 12 months post TB treatment initiation provided an opportunity to firstly evaluate sustainability of the QI intervention effect on CFR within a feasible time frame, secondly to observe whether the impact on TB case fatality was sustained after withdrawal of the intervention, and lastly to quantify the change in TB case fatality after QI withdrawal. Furthermore, the additional follow-up provided an opportunity to uncover excess mortality not observed in the 12-month follow-up period within the SUTHI study primary analysis. This prespecified secondary analysis evaluated the impact of QI on CFR at 18-months in patients diagnosed with TB irrespective of HIV infection status.

Methods

Study design and participants

We conducted an open-label cluster randomized-controlled study between 2016 and 2018 in two districts in KwaZulu-Natal (KZN), South Africa. A PHC nurse together with the PHC clinics under his/her direct supervision comprised each cluster. Eight PHC nurse supervisors (n = eight clusters) supporting 20 clinics (total of 40 clinics in the study) were randomly assigned (1:1) to the QI intervention and standard of care (SOC) arms, respectively. The primary outcome of the SUTHI study was all-cause mortality at 12-months from enrolment among newly diagnosed HIV-TB co-infected patients.[14] Description of the cohort and study procedures are published elsewhere.[5,14] In this pre specified secondary analysis of the SUTHI study, we assessed 18-month CFR outcomes of newly diagnosed TB patients irrespective of HIV status.

Ethics

The University of KwaZulu-Natal Biomedical Research Ethics Committee (UKZN BREC) approved the study, with waiver of participant informed consent {(ref no. BF108/14) and Clinicaltrials.gov, NCT02654613, registered 01 June 2015}.

Blinding, masking and randomization

Using a master list of eligible PHC nurse supervisors and their respective clinics within the selected local health district, a statistician randomised PHC nurse supervisors in a 1:1 ratio using a computer-generated randomization code. As each PHC nurse supervisor managed multiple clinics, randomization at the PHC supervisor level helped reduce between-cluster contamination. No matching or stratification was used in the randomisation process. Matching based on geography or proximity is a common approach when designing cluster randomized trials. However, in this trial, some PHC nurse supervisors oversaw multiple clinics, with some located in rural areas and others in urban settings, making area-based matching unfeasible. Clinic staff were aware of arm allocation.

Procedure

Intervention clinics formed a QI collaborative, which met once every six months for learning sessions that consisted of QI methods training, best practice exchanges, and information sharing. Study staff provided in-person mentorship and coaching to QI sites between learning sessions, to improve clinic performance in implementing HIV-TB integrated services. Description of the QI intervention package and impact on measured target process indicators are published elsewhere.[5,14] Control clinics received the SOC support provided to all South African National Department of Health (NDoH) clinics for implementation of HIV and TB guidelines.[16,17]

Outcomes

This study evaluates 18-month CFR outcomes of newly diagnosed TB patients irrespective of HIV status, where CFR was defined as the proportion of patients known to have died among those diagnosed and initiated on TB treatment. In the analysis of CFR, patients who were lost to follow-up are considered not to have died. Mortality data among TB patients were collected and confirmed

through death certificates, clinic documents, and from the South African Death registry. Patients were followed up from the enrolment date until death, hospital referral to another health facility, the last clinic visit date among those who were lost to follow-up or 18 months post enrolment. Vital status of TB patients with no recorded TB treatment outcomes were elicited from alternate sources including the ART program's electronic patient medical records and the South African national death registry. Definitions of TB treatment outcome follow prevailing South African national Department of Health (NDOH) guidelines.[16]

Data collection

Patient level data were collected from the Three Integrated Electronic Registers (TIER.NET) database commencing at TB program registration for each patient and thereafter up to a minimum of 18-months of follow-up. Patients participating in this study were 18 years of age or more; newly diagnosed with TB based on either smear or culture confirmation, radiologic evidence, or clinical diagnosis. Documented evidence of enrolment into HIV care or available results from two rapid HIV tests were used to determined HIV-infection status.[5,14] Tuberculosis and HIV clinical outcome indicators were generated monthly from electronic data management systems within the clinics. Data QI, quality assurance activities, and adherence to QI intervention by arm are published elsewhere.[5]

Statistical analysis

Sample size and power calculations were not carried out for this secondary analyses. The baseline demographic and clinical characteristics were summarized at individual level. Categorical variables were described as number and percentages, while continuous variables were summarized as medians and interquartile range (IQR). Patients who demised prior to TB program registration and treatment commencement were not included in this analysis. The corresponding 95% confidence interval (CI) for cluster-specific rates were calculated using the score test method. The CFR in each arm is the geometric mean or equivalently, arithmetic mean of logarithmic (log) rates across individual clusters. The arm-specific 95% CI were based on t-distribution with 14 degrees of freedom.

An overall adjusted rate ratio was calculated using two-stage approach based on cluster level summaries. The following covariates were included in the analyses: age at TB treatment initiation, gender, TB disease classification, HIV or ART status and geographical area (urban or rural) where clusters were located. These variables were previously shown to be associated with death among patients diagnosed with TB in the same setting.[18,19] In the first stage, we ignored the clustering at PHC supervisor level and used multivariable logistic regression analyses of death with all the covariates included in the model except for the study arms, to obtain the ratio of observed to expected deaths (ratio-residual) for each cluster. While this study used logistic regression analysis, the two-stage analytical approach effectively produces risk ratios rather than odds ratio.[20] In the second stage, we calculated adjusted ratio as the ratio of the arithmetic means of the ratio-residuals for the clusters in each arm. The variance of the adjusted rate ratio was calculated using Taylor series approximation and this was used to construct the 95% confidence interval for the rate ratio, based on t-statistic with 14 degrees of freedom.

We performed an exploratory and used generalized estimating equations (GEE) for binary model with an exchangeable covariance structure to calculate odds ratios. These models do not perform robustly when there are fewer number of clusters per arm and therefore, herein, they are not used to make inferences about the effectiveness of the intervention but to determine if the characteristics are associated with TB-related death in a conditional model. Most importantly, we evaluated whether any interactions between (i) study arm and other variables used in the model; (ii) between any of the two variables needed to be incorporated into the model and only kept those that were statistically significant. These models incorporate clustering by the PHC clinic supervisor conditional on age, sex, an interaction between age and sex, TB disease classification, area where clinic is located and HIV or ART status. The statistical analysis was conducted in SAS version 9·4.

Role of funding source

The funders, South African Medical Research Council (SAMRC), and UK Government's Newton Fund through the United Kingdom Medical Research Council (UKMRC) had no role in the study design, study execution, analyses, data interpretation, or decisions to submit the study findings for publication.

Results

Between December 2016 and December 2018, a total of 5817 TB patients were diagnosed with TB, 59·7% (3473) in the intervention arm and 40·3% (2344) in the control arm. The average number of patients per cluster was 434 (range 36–1183) and 293 (range 17–622) in the intervention and control arms, respectively (Fig. 1). The median follow-up time per participant per cluster was 87 weeks (IQR: 38–140) in the intervention arm and 88 weeks (IQR: 44–158) in the control arm. Within the intervention and control arms at baseline: median participant age (years) was 36 (IQR: 28–46) and 35 (IQR: 27–47) respectively; with 47·0% (163,445) and 68·9% (16,213) residing in rural communities, respectively (Table 1). In both study arms >50% of TB patients were male and >70% were 26–45 years of age. The proportion of patients that are HIV negative; PLWHA initiated on

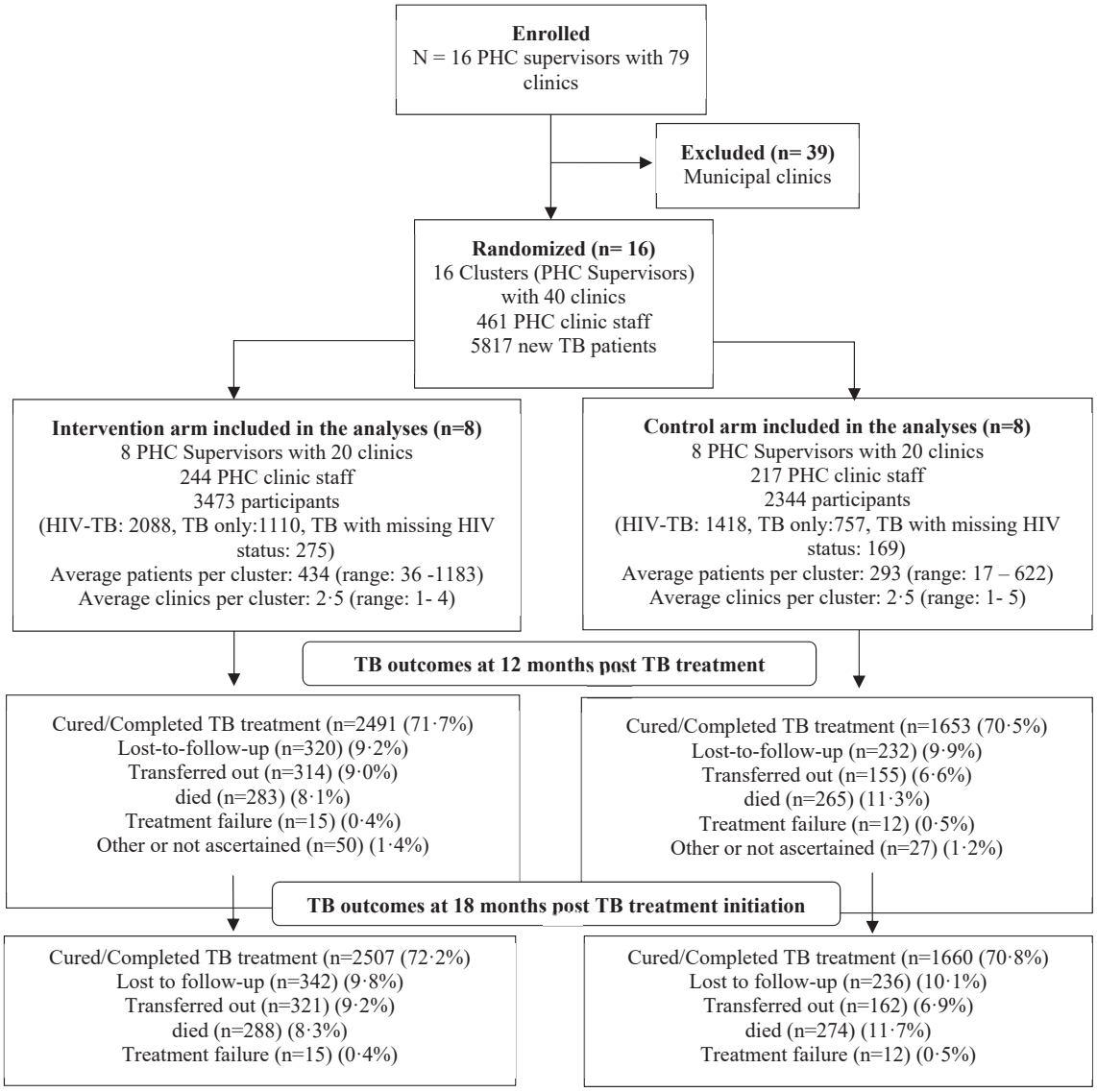


Fig. 1: Randomization and follow-up of HIV-TB co-infected and TB only participants attending PHC clinics that were supervised by 16 PHC nurse supervisors (clusters) in the SUTHI.

ART; PLWHA not on ART; and those with unknown HIV or ART status was similar between study arms. Among those PLWHA initiated on ART, 60·9% (1186) in the intervention arm and 63·4% (854) in the control arm were already on ART at the start of TB treatment (Table 1).

Case fatality rates at 18 months of study enrollment in intervention and control arms

We observed a total of 562 deaths among newly diagnosed TB patients, n = 288 in the intervention arm and n = 274 in the control arm (Fig. 1). Case fatality rate by arm was 9·5 [95% confidence interval (CI): 6·9–12·9] and 11·3 (95% CI: 8·7–14·7)] in the intervention and control arms, respectively (adjusted rate ratio, 0·9 (95% CI: 0·6–1·2) (Table 2). We did not observe a significant reduction in CFR within intervention compared to control arm clinics. Among those who died, the median time to death post TB treatment initiation in the intervention and control arms were 87 days (IQR: 38–140) and 88 days (IQR: 44–158) respectively. Among all the deaths observed in intervention and control arms: 255 (88·5%) and 245 (89·4%) occurred within six months of TB treatment initiation, while 28 (9·7%) and 20 (7·3%) died between 6 and 12 months of TB treatment initiation, respectively (Supplementary Figure S1). Cluster-

Characteristics	Category	Intervention arm (n = 3473)	Control arm (n = 2344)
Mean (range) patients per cluster		434 (36–1183)	293 (17–622)
Median (IQR) age (years) at TB treatment initiation		36 (28–46)	35 (27–47)
Age group (years) n (%)	<5	52 (1·5%)	52 (2·2%)
	5–15	81 (2·3%)	78 (3·3%)
	16–25	535 (15·4%)	369 (15·7%)
	26–35	1063 (30·6%)	689 (29·4%)
	36–45	852 (24·5%)	506 (21·6%)
	46–55	465 (13·4%)	324 (13·8%)
	56–65	263 (7·6%)	211 (9·0%)
	>65	162 (4·7%)	115 (4·9%)
Gender n (%)	Male	2031 (58·5%)	1383 (59·0%)
TB disease classification n (%)[d]	Extra Pulmonary TB	523 (15·1%)	266 (11·4%)
	Pulmonary TB	2949 (84·9%)	2077 (88·6%)
HIV status n (%)	HIV negative	1110 (32·0%)	757 (32·3%)
	PLWHA	2088 (60·1%)	1418 (60·5%)
	Unknown HIV status	275 (7·9%)	169 (7·2%)
	Unknown ART/HIV status[a]	417 (12·0%)	239 (10·2%)
ART status among PLWHA, n (%) [3506]	Initiated on ART	1946 (93·2%)	1348 (95·1%)
	PLWHA, not on ART	15 (0·7%)	18 (1·3%)
	PLWHA, no ART data	127 (6·1%)	52 (3·7%)
ART start relative to TB treatment among PLWHA, n (%) [3294]	Started ART before TB treatment	1186 (60·9%)	854 (63·4%)
	Started ART during TB treatment	728 (37·4%)	471 (34·9%)
	Started ART after TB treatment completion	32 (1·6%)	23 (1·7%)
Viral load (copies/ml)[b] within 12 months before TB treatment initiation n (%)	Viral load ≤200 copies/ml	1070 (30·8%)	710 (30·3%)
	Viral load >200 copies/ml	398 (11·5%)	335 (14·3%)
	Missing viral load data	478 (13·8%)	303 (12·9%)
District, n (%)	KCD	1714 (49·4%)	1011 (43·1%)
	Ugu	1759 (50·6%)	1333 (56·9%)
Area, n (%)[c]	Rural	1634 (47·0%)	1613 (68·8%)
	Urban	1839 (53·0%)	731 (31·2%)

Abbreviations: PLWHA: People living with HIV/AIDS; IQR: interquartile range. [a]Unknown HIV status, PLWHA not on ART, PLWHA no ART data. [b]The highest measured HIV viral load from 12 months before TB treatment initiation. [c]Classification of clinics into urban and rural was from a pre-exiting DoH classification received from the respective district office. [d]Two participants with missing data.

Table 1: **Baseline clinical and demographic characteristics.**

specific case fatality rates (CFR) ranged between 6·1% (95% CI: 4·9–7·6) and 18·9% (95% CI: 13·3–26·1) in the intervention arm and 6·9% (95% CI: 4·6–10·2) and 15·1% (95% CI: 11·4–19·8) in the control arm, respectively (Fig. 2). Overall between–cluster coefficient of variation (CV) derived across all 16 clusters was 0·3.

Case fatality rates in the intervention and control arms among HIV-negative patients were 5·7% (95% CI: 3·6–9·1) and 4·3% (95% CI: 3·2–5·8), and among PLWHA on ART was 10·8% (95% CI: 7·8–14·7) and 14·4% (95% CI: 9·3–22·4), respectively. Case fatality rates in the intervention and control arms among patients with unknown HIV or ART status was 13·8% (95% CI: 7·1–26·8) and 17·7% (95% CI: 12·2–25·9) vs 18·6% (95% CI: 9·1–38·0) and 33·0% (95% CI: 16·2–67·3) in known PLWHA with unknown ART status, respectively (Table 2). In HIV-TB coinfected patients CFR in the intervention and control arms: was 6·5 (95% CI: 3·6–11·6) and 11·5 (95% CI: 6·5–20·0) in those on ART with viral loads <200 copies/ml and 22·4 (95% CI: 16·7–30·2) and 19·7 (95% CI: 11·3–34·5) in those with no viral load data as they commenced ART within 12 months before initiating TB treatment, respectively.

Case fatality rates disaggregated by gender was 6·9% (95% CI: 3·9–12·0) and 11·2% (95% CI: 9·0–14·0) among females and 11·0% (95% CI: 8·0–15·3) and 11·2% (95% CI: 8·2–15·4) among males in the intervention and control arms, respectively (Table 2). In both arms, CFR increased with increasing age, from 4·7% to 23·3% in the intervention arm, and 4·6% to 32·9% in the control arm in 16–25 and greater than 65-year-old patients, respectively. Case fatality rates in both urban and rural communities were similar across study arms.

Characteristics	Overall	Intervention arm			Control arm			Adjusted Rate Ratio (95% CI)
	Case fatality rate (95% CI) (%)[a]	No. diagnosed with TB	No. of deaths	Case fatality rate (95% CI) (%)	No. diagnosed with TB	No. of deaths	Case fatality rate (95% CI) (%)[a]	
Overall	10·3 (8·6–12·4)	3473	288	9·5 (6·9–12·9)	2344	274	11·3 (8·7–14·7)	0·9 (0·6–1·2)
Gender								
Female	8·9 (6·8–11·8)	1442	98	6·9 (3·9–12·0)	961	105	11·2 (9·0–14·0)	
Male	11·1 (9·1–13·6)		190	11·0 (8·0–15·3)	1383	169	11·2 (8·2–15·4)	
Age groups (years)								
<5[b]	–	52	3	–	52	0	–	
5–15[b]	–	81	2	–	78	2	–	
16–25	4·6 (3·3–6·5)	535	23	4·7 (2·5–8·8)	369	17	4·6 (2·7–7·6)	
26–35	7·1 (4·9–10·3)	1063	60	5·5 (3·1–9·7)	689	68	9·1 (5·1–16·3)	
36–45	10·3 (8·4–12·7)	852	72	10·1 (6·9–14·6)	506	61	10·7 (8·0–14·3)	
46–55	15·7 (10·8–22·8)	465	59	14·3 (9·7–21·1)	324	51	17·2 (8·1–36·6)	
56–65	16·5 (12·2–22·5)	263	36	15·8 (10·5–23·9)	211	44	17·2 (9·5–31·2)	
>65	27·7 (18·9–40·6)	162	33	23·3 (12·0–45·3)	115	31	32·9 (19·3–56·0)	
TB disease classification								
Extra Pulmonary TB	15·4 (11·2–21·0)	523	68	16·0 (10·7–24·1)	266	37	14·8 (8·3–26·3)	
Pulmonary TB	9·6 (7·7–12·1)	2949	220	8·5 (5·9–12·3)	2077	236	11·1 (8·0–15·5)	
HIV, ART status								
HIV negative	5·0 (3·9–6·5)	1110	55	5·7 (3·6–9·1)	757	38	4·3 (3·2–5·8)	
Initiated on ART	12·4 (9·7–16·0)	1946	179	10·8 (7·8–14·7)	1348	188	14·4 (9·3–22·4)	
Unknown ART/HIV status or missing ART initiation date[b]	18·7 (14·2–24·7)	417	54	16·3 (10·1–26·4)	239	48	21·1 (13·8–32·1)	
PLWHA, no ART data	24·1 (15·4–38·0)	127	18	18·6 (9·1–38·0)	52	14	33·0 (16·2–67·3)	
PLWHA, not on ART[c]	–	15	5	–	18	6	–	
Unknown HIV or ART status	15·8 (11·6–21·6)	275	31	13·8 (7·1–26·8)	169	28	17·7 (12·2–25·9)	
Viral load at 6 months post-TB treatment initiation (copies/ml)[d]								
Viral load ≤200 copies/ml	8·6 (5·9–12·7)	1070	50	6·5 (3·6–11·6)	710	75	11·5 (6·5–20·0)	
Viral load >200 copies/ml	12·4 (9·1–16·8)	398	42	11·8 (7·7–18·1)	335	44	13·1 (7·0–24·5)	
Missing viral load data	21·8 (16·9–28·2)		87	22·4 (16·1–31·1)	303	69	21·3 (12·8–35·4)	
Missing viral load data in ART start <12 months[e]	21·0 (16·1–27·6)	393	73	22·4 (16·7–30·2)	257	54	19·7 (11·3–34·5)	
Area								
Rural	12·4 (10·7–14·3)	1634	179	11·8 (8·3–16·6)	1613	215	12·9 (11·1–14·9)	
Urban	6·1 (4·4–8·4)	1839	109	6·0 (4·5–8·0)	731	59	6·2 (1·5–25·1)	
District								
KCD	10·4 (7·9–13·8)	1714	139	10·2 (5·9–17·5)	1011	114	10·8 (6·6–17·4)	
Ugu	10·2 (7·4–14·2)	1759	149	8·4 (4·4–16·2)	1333	160	11·9 (6·6–21·2)	

Abbreviations: PLWHA: People living with HIV/AIDS; CI: confidence interval. [a]The case fatality rate is the geometric mean of the rates of individual clusters. [b]Unknown HIV status, PLWHA not on ART, PLWHA no ART data. [c]Where we have less than ten events, case fatality rates were not calculated to avoid presenting very wide 95% CIs. [d]The highest measured HIV viral load within six months after the end of TB treatment. [e]People with missing viral load data who started ART at any point up to 12 months before initiating TB treatment.

Table 2: **Effect of QI intervention on TB case fatality rates among participants with TB irrespective of HIV coinfection in intervention and control arm clusters.**

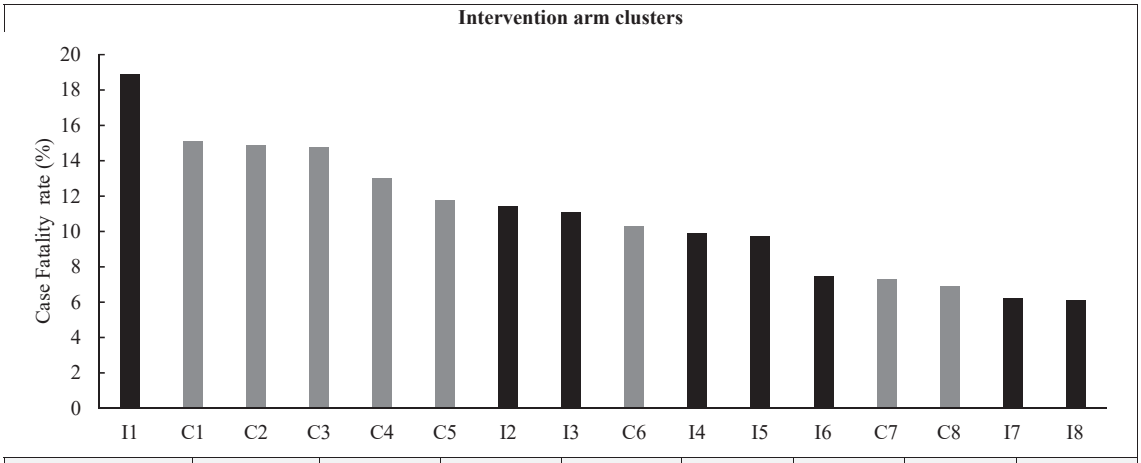
However, rates in rural communities were two-fold higher than rates observed in urban communities (Table 2).

Tuberculosis treatment outcomes excluding death

Overall TB treatment outcomes in the intervention and control arms were cure–9·6% and 7·4%; treatment completed- 57·2% and 57·6%; lost to follow-up–4·3% and 3·9%; transfer out–10·1% and 6·5%; and treatment failure–0·2% and 0·1%, respectively. Cluster-specific TB outcomes in the intervention and control arms are shown (Fig. 3).

Risk factors associated with death among patients initiated on TB treatment

The interaction terms between the study arm and other variables were evaluated and found to be statistically insignificant except for the interaction between age and gender which was statistically significant. Patients who are HIV-negative compared to PLWHA on ART had



Clusters	I1	I2	I3	I4	I5	I6	I7	I8
Cluster size	143	245	36	283	832	107	644	1183
Case fatality rate (%) (95 % CI)	18·9 (13·3-26·1)	11·4 (8·0-16)	11·1 (4·4-25·3)	9·9 (6·9-13·9)	9·7 (7·9-11·9)	7·5 (3·8-14·1)	6·2 (4·6-8·3)	6·1 (4·9-7·6)
Control arm clusters								
Clusters	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**
Cluster size	278	175	203	622	17	593	123	333
Case fatality rate (%) (95 % CI)	15·1 (11·4-19·8)	14·9 (10·3-20·9)	14·8 (10·6-20·3)	13·0 (10·6-15·9)	11·8 (3·3-34·3)	10·3 (8·1-13)	7·3 (3·9-13·3)	6·9 (4·6-10·2)

Fig. 2: Cluster-specific case fatality rates in the intervention (I) and control (C) groups among all participants with TB irrespective of HIV co-infection. The black and grey color represents clusters in the intervention and control arms, respectively. Abbreviation: CI: Confidence interval.

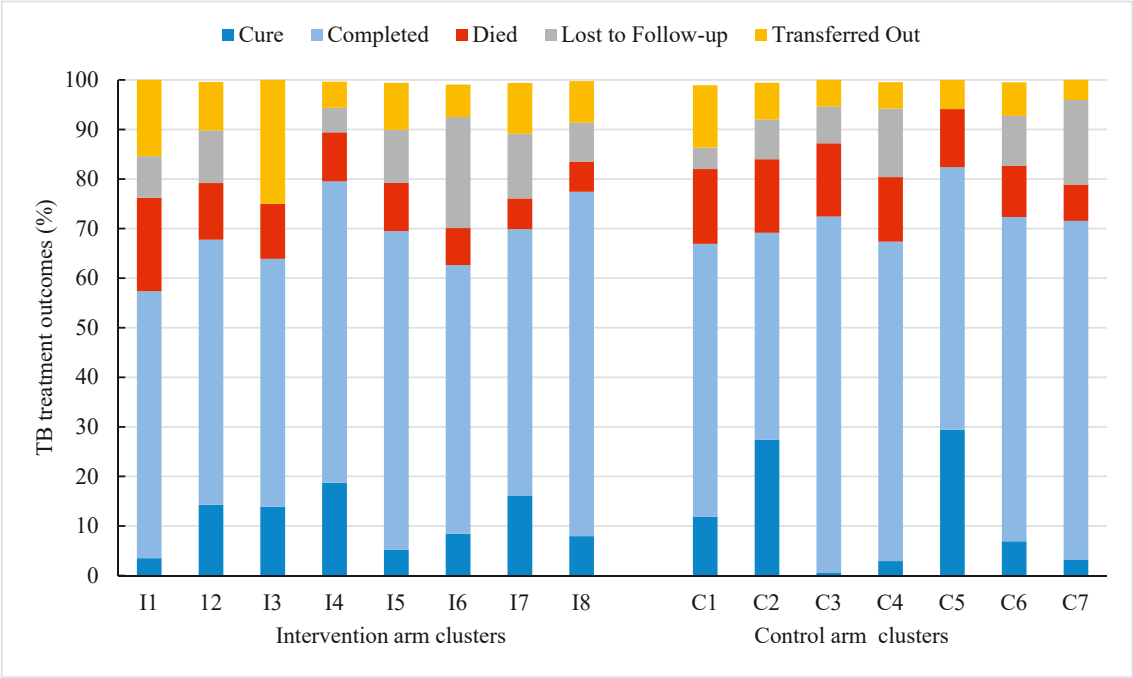
70% lower likelihood of death [adjusted odds ratio (aOR) 0·3 (95% CI: 0·2–0·42)]. However, PLWHA with missing ART data or those not on ART have increased odds of death compared to patients on ART (Supplementary Table S1). We observed lower case fatality rates among younger males and older females (Supplementary Figure S2), however, a complex model with interaction term between age and gender showed that younger women have increased odds of death compared to younger men (Supplementary Table S1). Using parameter estimates from a complex model we demonstrate that at 25, 50 and 60 years of age the aOR was 1·3 (95% CI: 0·9–1·8); 0·7 (95% CI: 0·6–0·8); and 0·5 (95% CI: 0·4–0·6) in women compared to men.

Discussion

In this secondary analysis evaluating the impact of QI activities on TB associated mortality at 18-months follow-up, we demonstrate high CFR exceeding 10% among newly diagnosed TB patients irrespective of HIV co-infection status. However, we did not observe a significant reduction in TB CFR in the intervention compared to control arm clinics. Quality improvement aimed at optimizing quality of TB care, improved coverage of TB services, and scaling up best practice in integrated treatment provided greater survival benefit for specific participant subgroups such as PLWHA on ART, females, and those residing in urban areas, albeit not statistically significant. In addition to being male older than 50 years, our data demonstrated ART naïve PLWHA or HIV-TB coinfected patients recently commencing ART, unknown ART status, and living in a rural area were risk factors for TB associated mortality.

There is a scarcity of published data reporting the impact of QI on TB associated mortality, hence it is likely that this is the first study demonstrating lower mortality among diagnosed TB patients irrespective of HIV infection following a QI intervention. We observed the highest CFR in the first six months of TB therapy in both study arms. While cause of death is unknown for these patients, these deaths are likely due to advanced HIV, extensive or disseminated TB disease, undiagnosed TB drug resistance, or the presence of clinical co-morbidities including co-infections.

Furthermore, while PLWHA on ART receiving QI services demonstrate greater, though non-significant, survival benefit, our finding of high TB CFR among HIV negative patients within the intervention arm remains poorly understood within TB programs. A systematic review conducted over eight years in South Africa among patients accessing TB treatment, reported a 26·4% overall TB mortality rate, showing three-fold and four-fold higher mortality rates among HIV negative patients and PLWHA on ART, respectively.[18] It is noteworthy that despite greater linkage to care and access to integrated HIV and TB services, the risk of mortality was similar for both PLWHA on ART and



	Intervention arm estimate (95% CI)	Control arm estimate (95% CI)
Cure	9·6% (5·8 - 15·8)	7·4% (2·2 - 24·7)
Treatment completed	57·2% (52·0 - 62·8)	57·6% (49·1 - 67·5)
died	9·5% (6·9 - 12·9)	11·3% (8·7 - 14·7)
Lost-to-Follow-up	4·3% (0·5 - 34·0)	3·9 % (0·5 - 29·9)
Transferred Out	10·1% (6·7 - 15·1)	6·5% (4·9 - 8·6)
Treatment Failure	0·2% (0·0 - 0·9)	0·1% (0·0 - 0·8)

Fig. 3: Cluster-specific and overall TB treatment outcomes with 95% CI in the intervention and control arms among all participants with TB irrespective of HIV co-infection. Abbreviation: CI: Confidence interval.

those HIV-negative.[18] A South African retrospective chart review reported higher TB mortality rates overall with mortality being approximately three-fold higher among HIV-TB coinfected patients.[21] Despite South African NDoH clinical and programmatic efforts to address the needs of key and vulnerable populations, these unacceptably high mortality rates among TB patients including those who are HIV negative and PLWHA on ART, highlight suboptimal access to quality TB services. High TB associated mortality rates among PLWHA and those who are HIV-negative have also been reported in Kenya at 17·7 and 7·3 per 100 person years, respectively.[22]

While mortality rates among HIV-TB co-infected patients are widely published, longitudinal data on the impact of HIV viral load on TB associated mortality is limited. We observed a two-fold lower CFR in virally suppressed PLWHA in the QI intervention arm compared to the control arm, likely reflecting the cumulative benefits of QI directed to delivering HIV-TB integrated services. Additionally, we observed considerably higher CFR in both study arms among PLWHA with no viral load data likely due to them starting ART in the 12 months before TB treatment initiation. Although these data are not statistically significant, it highlights the increased mortality risk resulting from a new TB episode in PLWHA not yet on suppressive ART. Similar findings were observed in a South African HIV-drug resistant-TB cohort where authors observed a significantly higher risk of poor TB treatment outcomes including death in viraemic patients (became detectable or were never suppressed) compared to those who maintained viral suppression.[23]

Our study findings of higher TB CFR in males compared to females overall and a trend of increasing TB associated mortality by increasing age in both males and females older than 26 years, peaking at age older than 65 years reflect global mortality trends.[1] Regardless of ethnicity or geographic location, published literature persistently report higher TB mortality rates in males in TB programs.[24–27] Mathematical modeling of South African data collected over approximately thirty years show that males contribute disproportionately to TB incidence

and mortality, likely due to lower health-seeking behaviour including failure to access routine TB screening, delayed diagnosis, and advanced disease at diagnosis.[19,28] Furthermore, the QI intervention had a greater impact in reducing mortality in females compared to males, likely due to the disproportionate representation of HIV in women and greater engagement of women in public health services. Factors such as increased engagement and uptake of HIV-TB health services, higher HIV-TB testing rates, improved adherence to TB treatment, and lower lost-to-follow-up rates among females contribute to the wide gender disparity in TB deaths.[19] Delayed health seeking behavior among males likely contributes to a higher proportion presenting with extensive TB disease at diagnosis. This complicated by age related comorbidities increases the risk of TB associated mortality.

We observed no deaths in males under 15 years of age, and more deaths in females compared to males in the 16-25-year age category. While mortality in females within sexually reproductive age categories has decreased globally, mortality from non-obstetric infections including TB is a major contributor to maternal morbidity and mortality.[29–31] An eight-year analysis of South Africa's National TB Register showed a 1·5 times greater TB mortality rate among women 15–24 years compared to similarly aged males likely due to the impact of HIV in young women. This study also found a 30% higher TB mortality rate among men older than 65 years compared to women.[19]

Similar to decades of published research showing the association of TB with a poor socio-economic status, we also observed a higher TB CFR among patients in poor rural communities compared to urban communities.[32,33] The prevailing socioeconomic disparity within communities highlights that targeted resource allocation and health system strengthening is required in vulnerable settings, for improved TB screening, testing, diagnosis, linkage to care, and treatment support. Rural communities are also plagued by social and structural barriers that drive the TB disease burden including poverty and food insecurity. This coupled with fewer health facilities that are overcrowded, under-resourced, and geographically dispersed undermines optimal TB service delivery and contributes to ongoing high rates of TB mortality.[32–35]

Our study found disproportionately higher CFR in males older than 50 years, TB patients living in rural areas, and viremic PLWHA i.e. ART naïve or HIV-TB coinfected patients recently commencing ART, and PLWHA with unknown ART status. There is clearly a need for close clinical observation and early triage of this subgroup of TB patients who are at high risk for mortality. While policy and program guidelines recommend HIV testing, ART initiation, and viral suppression in all PLWHA including those coinfected with TB, strategies to enhance greater demand for services and stronger HIV/TB program implementation targeting rural clinics, older males and vulnerable PLWHA is necessary to address population groups at higher risk for mortality. Consideration for inclusion of QI interventions, and regular outreach support within HIV and TB programs will help strengthen service delivery in rural clinics. In a setting with high TB mortality in men above 50 in the context of an ageing HIV population, expanding non-communicable disease (NCD) health services to also offer HIV and TB testing, treatment, and preventative care is essential. The impact of differentiated HIV and TB service delivery tailored for close clinical observation targeting those at higher risk for HIV or TB mortality requires evaluation. Furthermore, social relief grants aimed at supporting newly diagnosed TB patients is a strategy worth exploring. Despite freely available TB services, TB affected households and individuals face catastrophic costs that continues to be an impediment to favorable TB outcomes including survival. While empiric data from operational research and impact evaluations are limited, modelling studies suggest that expanded social protection is a key intervention to reduce TB incidence and mortality.

We acknowledge several limitations in this study. Tuberculosis associated mortality is likely underestimated due to several factors. Firstly, lack of unique patient identifiers that facilitate linkage of patients between public databases and facilities may have resulted in CFR underestimation. Secondly, poor routine clinic data management systems including delayed health systems' responsiveness to tracing lost-to-follow-up patients have undermined accurate estimates of TB CFR. We attempted to minimize underestimation of TB associated mortality through cross-linking those with unknown TB outcomes to notifications in the national death register. However, it is possible that not all TB deaths were accounted for due to failure to record and report deaths. The TB CFR by cluster should be interpreted with caution given the wide variation of cluster size across the study and differences in socio-economic factors. The combination of a smaller effect size (10%), fewer clusters (eight per arm) that were varying in size (n = 17 to 1183), a moderate coefficient of variation of cluster sizes (CV = 0·3) yielded a post-hoc statistical power of approximately 20%. This was an analysis of routine program databases hence missed visits were not easily identified and missing data could not be tracked and corrected.

Notwithstanding these limitations there are strengths in this study worth noting. This study was implemented through capacitating existing facility staff in delivering integrated HIV-TB services. Case fatality rates observed in this study reflect real world experiences with mortality in diagnosed TB patients at a community level. Furthermore, this study was conducted in both rural and urban health facilities where most patients in TB endemic resource limited settings

access care, thereby improving generalizability of our findings to similar settings. Our study highlights the need for tailored interventions guided by patient demographics to impact TB mortality. Our findings of ongoing high TB mortality despite TB and HIV diagnosis, linkage to TB treatment, and chronic ART care indicate that other unexplored factors contribute to ongoing TB mortality in our setting. Future research is required to better understand the impact of targeted health system strengthening on TB mortality including an evaluation of improved access to: TB laboratory services; trained personnel; and treatment support services. Evaluating the impact of strategies such as targeted universal testing for TB in rural communities with particular attention to congregate settings, periodic community-based TB screening and testing, TB diagnosis, and linkage efforts targeting men also warrants further investigation.

Despite a known TB diagnosis and established linkage to a health facility, one in ten patients with TB still died. Tuberculosis CFR was higher in males, those residing in rural communities, and highest among PLWHA not on ART and HIV-TB coinfected patients recently commencing ART Our data highlights the importance of identifying PLWHA, rapid ART initiation, achievement, and maintenance of viral suppression in addressing TB mortality in TB endemic settings. Furthermore, QI remains an important tool in addressing TB mortality in disease endemic settings, providing a potential solution for addressing implementation gaps toward achieving the 2035 End TB strategy targets.

Contributors

KN, AN, SSAK, NP, NYZ designed the study. KN is the grant holder. KN and MM drafted the manuscript. KN and SG led the study implementation, participant recruitment and data collection, with support from JN. NYZ and FM conducted statistical analysis. NYZ, FM, SG, and KN provided oversight on study data management. NYZ, FM, SG, and KN accessed, and verified data. NYZ, KN, RP, NP, MM, and FM analysed and interpreted all study data. All authors critically reviewed, this manuscript for important intellectual content and approved publication.

Data sharing statement

CAPRISA has an established procedure to make its research data more broadly available. Information on the process for requesting and obtaining data is available on the CAPRISA website (www.caprisa.org). Datasets used for the analyses for the CAPRISA research article that has been published, can be requested by any investigator through an online request lodged on the CAPRISA website the request will be assessed by the CAPRISA Scientific Review Committee, and once approved the datasets, study protocol and statistical analysis plan will be made available to interested investigators making the request. In line with standard data access principles, CAPRISA will ensure that metadata on the datasets and other relevant documents will be made available. Measures to ensure anonymization of participant data will be taken to protect individual and personally identifiable information in shared datasets. In addition, summary results of the trial will also be made publicly available in a timely manner by posting to the results section of the clinical trial registry and papers will be made available through UKZN's research space (for non-NIH studies) within 12 months of publication.

Declaration of interests

Kogieleum Naidoo, Santhanalakshmi Gengiah, Nonhlanhla Yende-Zuma, Nesri Padayatchi, and Salim S. Abdool Karim report grants from Newton Fund through UKMRC and SAMRC, during the conduct of the study. Andrew Nunn reports a grant for travel and subsistence costs from Janssen Pharmaceuticals during the conduct of the study. The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103151.

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